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EDITORIAL COMMENT

Good Fat, Bad Fat

The Increasingly Complex Interplay of Adipose Tissue and the Cardiovascular System*

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Obesity is present in more than 30% of adults in the United States and is a known risk factor for a variety of cardiovascular problems, including coronary artery disease, atrial fibrillation, congestive heart failure, and stroke (1). Obesity is considered to be present when there is an excess mass of adipose tissue in the body. There is now widespread acceptance of the notion that regional fat stores might have specific local or systemic effects. The best-known example of a local fat depot with a specific effect is the case of excess fat within the abdominal cavity, which seems to contribute to insulin resistance, raised blood pressure, and dyslipidemia. This constellation of features is referred to as the metabolic syndrome (2).

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The liberation of inflammatory molecules from visceral fat is thought to be a key factor in the development of the metabolic syndrome (2). Interestingly, the adverse effects associated with excess visceral fat are not observed or are much less pronounced in adults with only excess subcutaneous fat (2). The divergent properties of visceral and subcutaneous fat highlight the importance of understanding the unique biological properties of various depots of adipose tissue.

The specific effects of localized fat pools seem to be mediated by endocrine or paracrine actions of fat-secreted hormones or signaling molecules (3). These hormones or molecules, known as adipokines, include "beneficial" molecules such as adiponectin, which produces vasorelaxation and putative antiatherogenic effects (2,4). Adipose tissue can also secrete "unfavorable" cytokines, including tumor necrosis factor alpha, interleukin-6 and -8, and monocyte chemoattractant factor-1 (3,5). The elaboration of inflammatory cytokines is a potential pathway by which obesity could contribute to hypertension and atherosclerosis. Leptin is a fat-secreted hormone that might be both beneficial and detrimental, because it is important in appetite regulation, but also might increase sympathetic tone by central mechanisms, directly stimulate cardiac hypertrophy, and produce proinflammatory and proliferative effects on smooth muscle (6). It is provocative that a single tissue—fat in this case—can have seemingly opposite effects, depending upon its location and quantity.

Observations, such as those aforementioned, have triggered a wave of interest in the unique physiological and pathophysiological functions of different local depots of adipose tissue. Perivascular adipose tissue (PVAT) commonly encases or is adherent to large vessels such as the epicardial coronary arteries and the aorta and also many beds of smaller resistance vessels and microvessels. It has been hypothesized that PVAT might be involved in the development of cardiovascular diseases. For example, many groups have examined the hypothesis that epicardial fat might influence the development of coronary atherosclerosis (7). Because obesity is strongly associated with hypertension, the role of PVAT in the regulation of blood pressure is also of substantial interest (8).

Perivascular adipose tissue has previously been reported to block or attenuate the contractile response to vasoconstrictors (9). This so-called "anti-contractile" effect of PVAT seems to be mediated by paracrine mechanisms involving: 1) increased nitric oxide bioavailability, induced in part by fat-derived adiponectin; and 2) endothelium-independent pathways involving hydrogen peroxide generation (9–11). Thus, PVAT seems to have favorable effects that could lead to lowering of blood pressure in vivo. However, the waters are muddied by observations showing that the effect of "healthy PVAT" is lost in patients who are obese (9). Adiposopathy, or "sick fat," is considered to be present when fat contributes to cardiovascular disease (12). The loss of the anti-contractile effect of PVAT in systemic obesity was attributed to hypertrophy of adipocytes with resultant hypoxia, inflammation, and oxidative stress (9). One implication of that study is that there is an interaction or signaling mechanism between PVAT and other fat stores in the body and that PVAT might transition between a healthy and a sick state. One group has coined the term "vasocrine" signaling to describe the interaction between PVAT and adjacent vasculature (13).

The function of PVAT in relation to changes in total and regional body fat is the topic of an interesting new paper in this issue of the *Journal* by Aghamohammadzadeh et al. (14). They describe the effects of obesity and weight loss on the regulation of vascular contraction by PVAT. They performed studies using wire myography in isolated, endothelial-denuded microvessels obtained from biopsy of gluteal fat in subjects before and 6 months after bariatric surgery. Segments of the same artery were studied with and without the presence of PVAT. Histological and biochemical studies were also performed. Their main conclusions were that: 1) PVAT counteracts vasoconstriction by norepinephrine in normal weight subjects but not in obese subjects; 2) after bariatric surgery there is normalization of the PVAT "anti-contractile" function; and 3) the restoration of the normal protective effect of PVAT in subjects who have lost weight is attributable to

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a reduction in local inflammation and oxidative stress with improved adiponectin and nitric oxide bioavailability.

The findings of this study are intriguing for several reasons. First, a potential role of PVAT in clinically relevant disorders such as obesity-related hypertension is of great interest (8). The reason(s) for the high prevalence of resistant hypertension in obese subjects remain elusive. It is noteworthy that many studies have shown significant reductions in blood pressure accompanying modest weight loss, even when patients have not achieved a normal weight (15). These observations are reminiscent of those in the current study where normal vascular regulation by PVAT was restored after weight loss, despite the continuation of severe obesity. Perhaps regional fat pools, particularly PVAT, respond to weight loss interventions earlier than the larger areas of fat in the visceral and subcutaneous compartments. The finding that there was a dramatic (approximately 50%) reduction in the size of the PVAT adipocytes at a time when there was only a moderate loss of weight and persistent severe obesity (body mass index decreased from approximately 52 to 38 kg/m^2) supports this possibility. In keeping with this idea, prior studies have shown that visceral fat volumes are reduced more than subcutaneous fat volumes early after bariatric surgery (16). Likewise, it is well-established that diabetes improves or even resolves in some cases, very early after gastric bypass procedures, often before significant weight loss has occurred (17). This surprising effect is proposed to result from changes in hormonal signaling from the stomach and/or small intestine (17). The improvements in PVAT function relatively early after gastric bypass seen in the current study are reminiscent of the early reductions in blood pressure and the diabetes resolution and imply that normalization of total body fat is unlikely to be the key event necessary for other improvements in fat-related signaling to occur.

The authors hypothesize that PVAT takes on maladaptive or harmful characteristics when it is in a hypertrophied state characterized by fat cells with increased volume. According to this theory, the increased size of PVAT cells in obese individuals creates conditions of local hypoxia that leads to increased oxidative stress. This, in turn, accounts for a reduction in adiponectin release. Re-establishment of the anti-contractile effect of PVAT by exposure to superoxide dismutase formed the basis of this conclusion.

The main limitation of this paper is the use of small vessels isolated from subcutaneous fat, a depot not typically thought to play a role in the metabolic syndrome or in the pathogenesis of hypertension. Despite this limitation, the use of human tissue and the paired studies in the same individuals before and after gastric bypass surgery is a major strength of the current work.

The results of this study might lead us to consider interesting and exciting possibilities for novel therapeutic approaches involving pharmacological, genetic, or physical manipulation of local fat beds. For example, there is tremendous interest today in the dramatic blood pressure-lowering effects of renal artery "denervation" (18). Is it plausible that the efficacy of this procedure could be attributable in some part to the effects of radiofrequency ablation on the fat around the renal arteries or kidneys?

We now need to consider, on the basis of the results of the current study, not only the quantity of total body fat and the quantities of regional fat but also the effect of changes in fat stores leading to complex and dynamic interactions between the various fat pools and the cardiovascular system.

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